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polysaccharide antigens and *Streptococcus pneumoniae* protein antigens but are also drawn to immunological functional equivalents or transmembrane deletion variants of these antigens. There is no guidance provided in the specification as to how one would begin to choose these variants and thus it would require undue experimentation to make and use the claimed invention commensurate with the claims.

In response, Applicants note that the specification (see page 12, lines 17-26) teaches what is an "immunologically functional equivalent", that its meaning is clear to the skilled artisan, and hence it would not constitute undue experimentation to make the claimed invention as originally filed and understood by one skilled in the art. However, in order facilitate prosecution of this application, the claims have been amended.

With regards to "transmembrane deletion variants" Applicants respectfully note that the term is applied judiciously to specific protein antigens, and that transmembrane deletion variants to the claimed proteins are known in the art. The Examiner is respectfully directed to page 13, lines 10-16 of the specification where evidence of such transmembrane deletion variants are noted (Masure et al, noted below, also describe choline binding protein fragments). Applicants respectfully submit that they have provided sufficient guidance to enable one of skill in the art to make and use the claimed invention in a manner reasonable (in correlation) with the scope of the claims. For those reasons, Applicants respectfully submit that the amendments and remarks are sufficient to overcome this rejection and therefore request that this rejection be withdrawn.

#### **Claim Rejections – 35 U.S.C § 112, second paragraph**

Claims 1-9 and 11 are indefinite for failing to particularly point out and distinctly claim the subject matter which Applicant regards as the invention. The claims recite "immunologically functional equivalent", and it is unclear what Applicants are claiming.

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As noted above Applicants submit that the term, as defined in the specification, is clear and precise to one of skill in the art. Nevertheless, the amendments should make this rejection moot. Applicants respectfully request that this rejection is withdrawn.

Claims 1-9 and 11 are indefinite for failing to particularly point out and distinctly claim the subject matter which Applicants regard as the invention. The claims recite "transmembrane deletion variants" and it is unclear what Applicants are claiming.

As noted above, Applicants respectfully note that the term is applied judiciously to specific protein antigens, and that these transmembrane deletion variants are known in the art. The Examiner is respectfully directed to page 13, lines 10-16 of the specification where numerous examples of such transmembrane deletion variants are noted. It is respectfully submitted that the claims are clear and precise to one of skill in the art, and hence it is requested that this rejection be withdrawn.

#### **Claim Rejections - 35 U.S.C. §103**

Claims 1-6, 8-9 and 11 are rejected under 35 U.S.C. §103(a) as being unpatentable over Blake et al (Ref G, *U.S. Patent No. 5,866,135*) in view of Masure et al (Ref B, *U.S. Patent No. 6,245,335*). The claims are drawn to an immunogenic composition comprising at least one *Streptococcus pneumoniae* polysaccharide antigen, at least one *Streptococcus pneumoniae* protein antigen or immunogenically functional equivalent thereof and an adjuvant which is a preferential inducer of a TH1 response.

Blake et al teach immunogenic compositions include group A streptococcal polysaccharide covalently linked to protein or liposomes to form immunogenic conjugates. Blake et al teach that immunogenic compositions of the invention are conjugated to native or recombinant bacterial protein (carriers) such as tetanus toxoid, diphtheria toxoid or CRM 197. Blake et al teach that the immunogenic compositions are useful as a vaccine and may further comprise an

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adjuvant such as aluminum hydroxide, aluminum phosphate, monophosphoryl lipid A, QS21 or stearyl tyrosine.

Masure et al. teach a vaccine comprising choline binding proteins (CBPs) or fragments thereof. The Examiner concludes that it would be prima facie obvious at the time the invention was made to add the CBP vaccines of Masure et al to the group A streptococcal polysaccharide compositions as taught by Blake et al.

Applicants respectfully disagree. Blake et al. do disclose a vaccine against Group A Streptococcus (GAS) that includes a GAS polysaccharide covalently linked to a protein or liposome to form immunogenic conjugates. Blake et al also disclose that an adjuvant may be added to the immunogenic composition, *but unlike the present invention, suggest that any known adjuvant would suffice*. That is, according to Blake et al, an adjuvant that is a preferential inducer of a TH2 response (e.g., aluminum hydroxide), is just as effective as an adjuvant which is a preferential inducer of a TH1 response.

Applicants further note that Blake et al. do not teach the addition of free, or unconjugated, protein to the disclosed immunogenic composition, which again *is in contrast to the claimed invention*.

In addition, it is further noted that Group A Streptococcus is a very different microorganism from Streptococcus pneumoniae. It has a different pathology and the polysaccharides are quite different in their physical properties. Hence it is not clear why one would combine the GAS polysaccharides of Blake et al with the CBPs of Masure et al.

Turning to Masure et al, Applicants respectfully note that as cited, this is not an effective reference, as it issued after Applicants' effective US filing date of 17 March 2000 (obtained from 35 U.S.C. §371 of PCT/EP00/02467). However, as it could be cited under 35 U.S.C.

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§102(e)/103, Applicants will address the concerns raised by the Examiner, to avoid a future rejection and thus facilitate prosecution of this application.

Masure et al. teach novel choline binding proteins as vaccines against *Streptococcus pneumoniae*. Masure et al teach that choline binding proteins and fragments thereof, DNA encoding choline binding proteins and fragments thereof, and antibodies to choline binding proteins and fragments thereof, are useful therapeutically (see abstract, summary of invention). The *essence of the invention* is that certain pneumococcal proteins (i.e., the choline binding proteins) are sufficient for conferring immunity to pneumococcal infections. *That is, there is no need to add other components such as pneumococcal polysaccharides*. This is consistent with the abstract, the summary of the invention, the examples, claims, and detailed description. However, in one brief passage cited by the Examiner (col. 14, lines 41-46), Masure et al. comment that in selecting a preferred vaccine candidate, one *may* need to consider testing choline binding proteins "alone or in combination or coupled to a capsular polysaccharide". Applicants respectfully submit that this is an invitation to conduct further experiments, and that Masure et al. do not teach the importance of polysaccharides plus proteins - for taken as a whole, this reference would teach to the skilled artisan that choline binding proteins *alone* are sufficient for developing a pneumococcal vaccine.

In addition, Masure et al. do not teach the addition of an adjuvant which is a preferential inducer of a TH1. Rather, Masure et al. teach the opposite, that alum (aluminum hydroxide, a preferential inducer of a TH2 response) is a suitable adjuvant!

Therefore, given the above remarks, Applicants respectfully submit that the claimed invention is not obvious over the teachings of Blake et al. with those of Masure et al. First of all, Applicants note that the references describe 2 different pathogens, and as such Applicants do not agree that it would be obvious to tie together the teachings of both references.

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Second and more importantly, even if the references were combined, Applicants respectfully submit that the Blake et al, in view of Masure et al. do not yield the claimed invention. Blake et al. do not teach the addition of free protein (unconjugated) to bacterial polysaccharides, and Blake et al. do not specifically teach an adjuvant which is a preferential inducer of a TH1 response. Masure et al. teach as a whole that choline binding proteins are a suitable alternative to polysaccharides in developing a pneumococcal vaccine. Also, Masure et al. mention an adjuvant which is a preferential inducer of a TH2 response, which is in contrast to the claimed invention.

Furthermore, Applicants have found that if one adds at least one *Streptococcus pneumoniae* protein (unconjugated) and an adjuvant which is a preferential inducer of a TH1 response to a *Streptococcus pneumoniae* polysaccharide, then one gets a surprisingly better immune response - better than the summation of its individual components. See for example Example 2 (page 35, lines 5-15) where such compositions were surprisingly more immunogenic. See also Examples 4 and 6 (the beneficial result of adding a Streptococcus pneumonia protein (unconjugated) and a TH1 adjuvant) which teach that the claimed invention stimulates the immune response by 2 means - (i) humoral response AND (ii) cell-mediated immunity. None of the references alone or in combination teach this enhanced effect and none of the references alone or combination teach stimulation of the immune response in the same manner as Applicants.

For these reasons, Applicants respectfully request that this rejection be withdrawn.

Claims 1-9 and 11 are rejected under 35 U.S.C. §103(a) as being unpatentable over Kuo et al (Ref A, *U.S. Patent No. 5,565,20*) in view of Masure et al (*U.S. Patent No. 6,245,335*). The claims are drawn to an immunogenic composition comprising at least one *Streptococcus pneumoniae* polysaccharide antigen, at least one *Streptococcus pneumoniae* protein antigen or immunogenically functional equivalent thereof and an adjuvant which is a

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preferential inducer of a TH1 response. Kuo et al teach a composition comprising immunogenic polysaccharide-protein conjugates and pneumolysin protein of *Streptococcus pneumoniae*. Kuo et al also teach that the conjugates of the invention may be bound to aluminum hydroxide, aluminum phosphate, QS21, monophosphoryl lipid A and deacylated monophosphoryl lipid A.

Masure et al are described above. The Examiner concludes that it would be *prima facie* obvious to add the CBP vaccines of Masure et al to the pneumococcal polysaccharide recombinant pneumolysin conjugate vaccines as taught by Kuo et al because Masure et al teach that one may administer the CBP vaccines in conjunction with one or more pharmaceutical compositions used for treating bacterial infection.

Applicants respectfully disagree. Applicants respectfully note that Kuo et al. teach pneumococcal polysaccharides conjugated to the *Streptococcus pneumoniae* protein pneumolysin. The "inventive concept" of Kuo et al. is that native pneumolysin, a toxin, is not detoxified prior to conjugation. That is, the conjugation process of pneumolysin to *S. pneumoniae* polysaccharide(s) results in a toxoided pneumolysin protein. As a result, Kuo et al. do not teach (i) a free or unconjugated pneumolysin (not necessary), or for that matter any other unconjugated protein that is combined with a polysaccharide-pneumolysin conjugate. Kuo et al. do teach that adjuvants can be added to the polysaccharide-protein conjugate(s), however, according to Kuo et al. there is no distinction between adjuvants that preferentially induce a TH1 response versus those that induce a TH2 response. That is, Kuo et al. teach (ii) *that any adjuvant can be used, which is in contrast to the claimed invention*. Thus Applicants respectfully submit that Kuo et al. do not teach a free or unconjugated protein in combination with pneumococcal polysaccharide conjugate(s) and Kuo et al. do not specifically teach the use of an adjuvant which is a preferential inducer of a TH1 response.

Masure et al has been addressed previously and does not correct the deficiencies of Kuo et al. That is, Masure et al. teach as a whole that *choline binding proteins are a suitable alternative to polysaccharides* in developing a pneumococcal vaccine. Also, Masure et al. *teach an*

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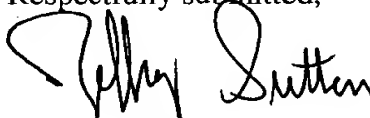
*adjuvant which is a preferential inducer of a TH2 response, which is in contrast to the claimed invention.*

Furthermore, none of the references alone or in combination teach an enhanced immune response when a polysaccharide + protein (free) + adjuvant (which is a preferential inducer of a TH1 response) is combined. Also, none of the references alone or combination teach stimulation of the immune response in the same manner (humoral response and cell-mediated immunity) as Applicants.

Thus, Applicants respectfully submit that the teachings of Kuo et al. in view of Masure et al. do not render the claimed invention obvious. For those reasons, Applicants respectfully request that this rejection be withdrawn.

Applicants respectfully submit that the aforementioned amendments and remarks are fully responsive to the Office Action and request reconsideration of the rejections stated therein. The Examiner is invited to contact Applicants' undersigned at the telephone number provided below if such might facilitate allowance of the pending claims.

Respectfully submitted,



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VERSION WITH MARKINGS TO SHOW CHANGES MADE

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In the Claims:

1. (Amended) An immunogenic composition comprising at least one *Streptococcus pneumoniae* polysaccharide-protein conjugate [antigen], at least one *Streptococcus pneumoniae* protein antigen [or immunologically functional equivalent thereof], and an adjuvant which is a preferential inducer of a TH1 response.
2. (Amended) The immunogenic composition of claim 1, wherein the protein antigen is an outer surface protein or a secreted protein of *Streptococcus pneumoniae* [or immunologically functional equivalents thereof].
3. (Twice amended) The immunogenic composition of claim 1, wherein the protein antigen is a toxin, adhesion or lipoprotein of *Streptococcus pneumoniae* [or immunologically functional equivalents thereof].
4. (Twice amended) The immunogenic composition of claim 1, wherein the protein antigen [or immunologically functional equivalent thereof] is selected from the group: pneumolysin, PspA or transmembrane deletion variants thereof, PspC or transmembrane deletion variants thereof, PsaA or transmembrane deletion variants thereof, glyceraldehyde-3-phosphate dehydrogenase, and CbpA or transmembrane deletion variants thereof.
5. Please cancel.
6. (Amended) The immunogenic composition of claim 1 [5], wherein the [carrier] protein conjugate is selected from the group consisting of: Diphtheria toxoid, Tetanus toxoid, CRM197, Keyhole Limpet Haemocyanin (KLH), protein derivative of Tuberculin (PPD), and protein D from *H. influenzae*.